50. (New) The method of claim 49, wherein said truncated Flk-1 receptor protein comprises a nucleotide sequence encoding amino acids 1 through 806 of Flk-1.

A4 CONT.

51. (New) The method of claim 49, wherein said truncated Flk-1 receptor protein comprises a nucleotide sequence encoding amino acids 1 through 806 of Flk-1 but lacking the 561 COOH-terminal amino acids of the intracellular kinase domain of Flk-1.

REMARKS

Claims 36-51 are pending in the present application. Claims 36-43 are amended. Amended claims 36, 42 and 49 have support on page 2, lines 13-18 and page 41, line 27 to page 42, line 1. Amended claim 38 is supported by the specification on page 41, lines 12--16. New claims 47, 48, 50 and 51 are supported by the original claims and the specification on page 41, lines 27-34. Claims 1-35 and 44-46 are canceled without prejudice or disclaimer as directed to non-elected subject matter. Applicants reserve the right to file one or more divisional applications on this canceled subject matter. Applicants acknowledge that the Examiner indicated that claim 43 is allowable if the rejection under 35 U.S.C.§ 1.112, second paragraph, is overcome.

Formal Matters:

1. Status of Related Applications

The status of the related applications have been indicated in the amendment to the specification page 1. It is requested that the objection to the specification be withdrawn.

2. Abstract

Applicants enclose a new abstract on a single sheet of paper with the Examiner's suggestions included in the text. Additionally, entry of the Abstract is requested above.

3. Title

The title has changed as requested by the Examiner and replacement of the present title is requested above.

4. Typographical Error

Claim 43 is objected to for the recitation of "administrating" rather than "administering." This typographical error has been corrected.

Obvious-type Double Patenting Rejection

Claims 36-41 are rejected under obvious-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,851,999. Applicants would like to hold this rejection in abeyance until allowable subject matter of the presently rejected claims has been indicated by the Examiner.

Objections and Rejections under 35 U.S.C. § 112, first and second paragrah

Claims 36-43

Claims 36-43 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in the recitation of "dominant-negative activity." The Examiner comments that the invention is drawn to truncated forms of the receptor which are signaling-incompetent and that the objected to phrase does not convey this subject. Although applicants do not acquiescence to this rejection as the specification defines this phrase, claims 36 and 42 have been amended to delete this phrase from the claims.

Claim 42 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because this claims is directed to an "isolated" receptor protein with "dominant-negative activity," but with the claim also reading on membrane-bound forms of the protein. The Examiner questions how a soluble protein can be signaling competent as well

as signaling incompetent. The Examiner appears to believe that the function of signaling or not signaling does not apply to the "soluble" form of the truncated Flk-1. Applicants respectfully traverse this rejection. Firstly, applicants have amended claim 42 to delete the word "isolated." But in response to the Examiner's questions, the truncated Flk-1 receptor protein is signaling incompetent because it is lacking the catalytic domain but this characteristic is not dependent upon whether the protein is soluble or membrane-bound but rather is dependent upon whether it has had all or portions of its domains deleted. The claimed truncated Flk-1 contains a functional extracellular domain that is located from the N-terminus of the protein and also contains the transdomain membrane (see page 41, line 35). The truncated Flk-1 can bind to VEGF in the cell, and thereby prevents this ligand from binding to the normal Flk-1 in the cell which inhibits the normal Flk-1. In view of these comments and the amendment to claim 42, it is requested that this rejection be withdrawn.

Claim 41 is rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled in that the claim recites that engineered cell line that contains a recombinant vector and produces infectious retrovirus particles expressing truncated Flk-1. The Examiner indicates that the retrovirus particles encode the truncated Flk-1 and there do not express a protein. Applicants have amended claim 41 to clarify that the retrovirus encodes the truncated Flk-1 and that the cell line expresses the truncated Flk-1. In view of the clarifying amendment, it is requested that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 36, 38 and 40-42 are rejected as being anticipated by Lemischka (U.S. 5,185,438 - herein after "the '438 patent). The Examiner alleges that the '438 patent discloses DNA encoding *flk-1* and vectors comprising the DNA. The Examiner further alleges that the '438 patent discloses soluble forms of the flk-1 receptor, as well as vectors encoding flk-1 in column 6. The Examiner alleges that soluble flk-1 would be expected to have a dominant negative activity which would inhibit the cellular effects of VEGF binding by competitively inhibiting such binding. The Examiner also submits that retroviral vectors are disclosed in column 9, line 67.

Applicants respectfully traverse this rejection and the Examiner's interpretation of the '438 patent. Applicants' claims are directed to vectors containing polynucleotides that encode a truncated Flk-1, to an isolated truncated Flk-1 and a method of inhibiting the cellular effects of VEGF by administering truncated Flk-1. The Examiner states that column 6 of the '438 patent discloses "soluble forms of the Flk-1 receptor" but applicants cannot locate this disclosure. It is noted that column 6, lines 15-19 of the '438 patent that the flk-1 contains the extracellular receptor domain but is lacking the transmembrane region and the catalytic domain. The claimed truncated Flk-1 has been amended to recite that it contains both the extracellular and transmembrane domain. Thus, the '438 patent fails to disclose the claimed truncated Flk-1 receptor proteins, and it follows that the disclosure of vectors containing polynucleotides cannot be interpreted as containing polynucleotides encoding truncated Flk-1 receptor proteins. Thus, applicants submit that the '438 patent fails to anticipate the pending claims. It is requested that this rejection be withdrawn .

Rejection under 35 U.S.C. § 103

Claims 36-42 are rejected as being obvious over Lemischka (U.S. 5,185,438 - herein after "the '438 patent), Matthews *et al.*("Matthews") and Termen *et al.* ("Termen") in view of Ulrich *et al.*("Ulrich"), Ueno *et al.*(including Ueno-1 and Ueno-2). The Examiner alleges that the '438 patent discloses soluble forms of the flk-1 receptor and vectors containing the DNA. The Examiner alleges that Matthews discloses a recombinant vector comprising cDNA which encodes Flk-1 in Figure 1. Further, the Examiner states that Matthews discloses that Flk-1 has strong homology to the c-Kit subfamily or receptor kinases, and in particular, to the Flt gene product. Further the Examiner alleges that Terman discloses cDNA encoding a receptor called KDR, the human homologue of Flk-1 determined on the basis of sequence homology. Terman is further used by the Examiner as disclosing that KDR encodes a receptor of VEGF.

The Examiner concludes that these three primary references teach that Flk-1 is a VEGF receptor falling into the class of type III tyrosine kinase receptors, with strong homology to the c-Kit family of receptors, and the insertion of the Flk-1 DNA into vectors. But the Examiner states that none of these three prior art teach or suggest construction of a recombinant vector encoding a truncated form of the disclosed Flk-1 meeting the claim

limitations, such as encoding amino acids 1-806 or other variants having extracellular and transmembrane domains but being signal incompetent.

The Examiner applies Ullrich and the two Ueno publications as disclosing three different receptor proteins that are truncated by the deletion of all or a portion of the sequence encoding the intracellular domain. The Examiner concludes that it would have been obvious for a person skilled in the art at the time of the invention was made to modify the nucleic acids and recombinant vectors of Matthews, Terman or the '438 patent to delete all or a portion of the sequence encoding the intracellular domain as taught by Ullrich or either of the Ueno publications. The Examiner finds motivation to combine the teachings of the six cited prior art from Terman's recognition that Flk-1 is the murine homolog of the KDR receptor and that it would be "desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF..." and further from the teachings of Ullrich and the Ueno publications.

Applicants respectfully traverse this rejection. Firstly, none of the primary references, Matthews, Terman or the '438 patent, disclose a truncated Flk-1 receptor protein containing a functional extracellular and transmembrane domain. The secondary references disclose three different receptor proteins, i.e., EGF, PDGFβ and FGFR, that lack a portion of the receptor. None of these secondary references suggest that they are related to the Flk-1 receptor protein or that they would behave the same as the claimed truncated Flk-1 receptor protein. Applicants submit that these prior art do not provide a suggestion to combine without the suggestion from applicants' own specification to prepare the claimed truncated Flk-1 receptor protein.

The Examiner has used impermissible hindsight to provide a motivation to combine the primary and secondary references to arrive at applications invention. When combining elements to make out a *prima facie* case of obviousness, the Examiner is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow*

Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Examiner has failed to support the alleged case of *prima facie* obviousness.

Obviousness "'cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.'" *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988), *citing ACS Hosp. Sys. v. Montefiore Hosp.*, 221 USPQ 929, 933 (Fed. Cir. 1984). It is applicants' position that neither the primary nor the secondary references provide a suggestion to truncate the Flk-1 receptor protein to arrive at the present invention.

At best, this obviousness rejection would be obvious "to try," a standard which has been rejected for purposes of determining obviousness under 35 U.S.C. 103. There must be a reasonable expectation of success to modify a prior art reference in a rejection under 35 U.S.C. § 103. In re Vaeck, 20 USPQ2d 1439 (Fed. Cir. 1991).

In view of the arguments provided above, it is requested that this rejection be withdrawn.

Allowable Subject Matter

The Examiner states that claim 43 would be allowable if the claims is amended to overcome the objection and rejection under 35 U.S.C. §112, second paragraph. Applicants believe that they have complied with the Examiner's request and have overcome this objection and rejection.

Conclusion

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to this effect is earnestly solicited. Should there be any questions concerning this application, Examiner Spector is invited to contact the undersigned at the number listed below.

Respectfully submitted,

Date May 14, 2003

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Marked-up Version of the Specification Showing Changes

Marked up version of 1st full paragraph on page 1, is below:

This application is a continuation-in-part of United States Application Serial No. 08/038,596, filed March 26, 1993, **now abandoned,** which is a continuation-in-part of United States Application Serial No. 07/975,750, filed November 13, 1992, **now abandoned,** both of which are incorporated by reference herein in their entirety.

Marked-up Version of the Claims Showing Changes

36. (Amended) A recombinant vector [containing] **comprising** a nucleotide sequence that encodes a truncated Flk-1 **having a functional Flk-1 extracellular and transmembrane domain** [which has dominant-negative activity] which inhibits the cellular effects of VEGF binding.

37. (Amended) The recombinant vector of claim 36[, containing] **comprising** a nucleotide sequence encoding amino acids 1 through 806 of Flk-1.

38. (Amended) The recombinant vector of claim 36 in which the vector is a retrovirus vector**, an adeno-associated viral vector and a herpes viral vector**.

39. (Amended) The recombinant vector of claim 38[, containing] **comprising** a nucleotide sequence encoding amino acids 1 through 806 of Flk-1.

40. (Amended) An engineered cell line that [contains] **comprises** the recombinant [DNA] vector of [Claim] **claim** 36 and expresses truncated Flk-1.

41. (Amended) An engineered cell line that [contains] **comprises** the recombinant vector of [Claim] **claim** 38 or 39 and produces infectious retrovirus particles [expressing] encoding truncated Flk-1**, wherein said cell line expresses truncated Flk-1**.

42. (Amended) A [isolated] recombinant truncated Flk-1 receptor protein **having a functional Flk-1 extracellular and transmembrane domain, wherein said protein** [which has dominant-negative activity which] inhibits the cellular effects of VEGF binding.

43. (Amended) A method of [modulating] **inhibiting** the cellular effects of VEGF in a mammal comprising [administrating] **administering** to the mammal an effective amount of truncated Flk-1 receptor protein which inhibits the cellular effects of VEGF binding.